Allogeneic cardiospheres delivered via percutaneous transendocardial injection increase viable myocardium, decrease scar size, and attenuate cardiac dilatation in porcine ischemic cardiomyopathy.

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Public Summary:
Epicardial injection of heart-derived cell products is safe and effective post-myocardial infarction (MI), but clinically-translatable transendocardial injection has never been evaluated. We sought to assess the feasibility, safety and efficacy of percutaneous transendocardial injection of heart-derived cells in porcine chronic ischemic cardiomyopathy.

Scientific Abstract:
BACKGROUND: Epicardial injection of heart-derived cell products is safe and effective post-myocardial infarction (MI), but clinically-translatable transendocardial injection has never been evaluated. We sought to assess the feasibility, safety and efficacy of percutaneous transendocardial injection of heart-derived cells in porcine chronic ischemic cardiomyopathy. METHODS AND RESULTS: We studied a total of 89 minipigs; 63 completed the specified protocols. After NOGA-guided transendocardial injection, we quantified engraftment of escalating doses of allogeneic cardiospheres or cardiosphere-derived cells in minipigs (n = 22) post-MI. Next, a dose-ranging, blinded, randomized, placebo-controlled ("dose optimization") study of transendocardial injection of the better-engrafting product was performed in infarcted minipigs (n = 16). Finally, the superior product and dose (150 million cardiospheres) were tested in a blinded, randomized, placebo-controlled ("pivotal") study (n = 22). Contrast-enhanced cardiac MRI revealed that all cardiosphere doses preserved systolic function and attenuated remodeling. The maximum feasible dose (150 million cells) was most effective in reducing scar size, increasing viable myocardium and improving ejection fraction. In the pivotal study, eight weeks post-injection, histopathology demonstrated no excess inflammation, and no myocyte hypertrophy, in treated minipigs versus controls. No alloreactive donor-specific antibodies developed over time. MRI showed reduced scar size, increased viable mass, and attenuation of cardiac dilatation with no effect on ejection fraction in the treated group compared to placebo. CONCLUSIONS: Dose-optimized injection of allogeneic cardiospheres is safe, decreases scar size, increases viable myocardium, and attenuates cardiac dilatation in porcine chronic ischemic cardiomyopathy. The decreases in scar size, mirrored by increases in viable myocardium, are consistent with therapeutic regeneration.